Altered beta-band activity across the basal ganglia thalamocortical network in a progressive model of Parkinson's disease

Eesha Bharti

Abstract

An increase in beta-band activity has been observed in the basal ganglia-thalamocortical (BGTC) network of Parkinson's patients, however, when beta-band oscillations change relative to visible PD motor symptoms and how it is changing across multiple nodes in the BGTC network with the increasing severity of PD remain unclear. Using simultaneously recorded local field potential activity from the BGTC network in a rhesus macaque, I observed changes in the low beta band (8-20 Hz) activity across multiple nodes in the network at the very mild stage of PD, where only a little or no motor signs were presented. A progressive increase in the high-beta band (21-35 Hz) in the STN and GP was observed corresponding with the increase in parkinsonian severity. Thus, results show that changes in low and high beta bands can be distinct from each other with the progression of parkinsonism. I hypothesize that these changes disrupt the motor function of the BGTC network, leading to the motor symptoms found in PD.

Introduction

Parkinson's disease (PD) is a progressive neurological disorder that consists of debilitating motor symptoms, such as bradykinesia, rigidity, and tremor.[1] These symptoms can be linked to a decrease in dopaminergic input to the basal ganglia (BG) causing changes in the basal ganglia thalamocortical (BGTC) loop, a neural network involved in many movement disorders.[2] Previous studies have found an increase in beta band oscillatory activity in the BGTC network that is thought to play a role in the expression of the motor symptoms of PD.[3]

Beta band oscillations (8-35 Hz) are associated with muscle contractions in the motor cortex, known to increase with motor control and decrease with changes in movement.[4] This excessive beta oscillation synchronization has been hypothesized to be a pathophysiological

marker of PD, which may disrupt communication between brain areas during movement.[5] The reduction of this activity with deep brain stimulation (DBS), together with the improvement of bradykinesia and rigidity, also supported the pathophysiological role of beta activity in PD.[6,7] It is currently unknown whether changes in beta activity precede or coincide with the onset of visible motor symptoms and how it is changing with the progression of PD in multiple nodes of the BGTC network. Determining the timing of oscillatory changes in both cortical and subcortical areas in the BGTC network allows for the identification of potential biomarkers related to different stages of PD, which would provide information to improve DBS and further determine its mechanisms of action.

I begin to address this gap in knowledge using a progressive nonhuman primate model of PD and prior simultaneous recordings of neuronal activity across multiple nodes in the BGTC network, including the motor cortex (M1), subthalamic nucleus (STN), and globus pallidus (GP). This approach provides a novel way to analyze the temporal changes of beta oscillations in multiple nodes in PD.

Methods

All procedures were approved by the University of Minnesota Institutional Animal Care and Use Committee and complied with US Public Health Service policies on human care and use of laboratory animals. A female rhesus macaque was rendered parkinsonian by systemic weekly or biweekly intramuscular injections (0.3-0.8 mg/kg) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

Behavioral assessment: The severity of PD symptoms was assessed using the modified Unified Parkinsonian Disease Rating Scale (mUPDRS), rating axial motor symptoms (gait, posture,

balance, and defense reaction) and appendicular motor symptoms (rigidity, bradykinesia, akinesia, and tremor). Scores were given on a 0-3 scale (0 as normal, 3 as severe) with the highest score being 39. 4 parkinsonian states were determined by assessing severity of parkinsonian symptoms through mUDPRS scores; 0-3 (State 1), 4-6 (State 2), 7-10.5 (State 3), >10.5 (State 4).

Neurophysiological recordings: Local field potential (LFP) signals were collected through 2 scaled-down 8-channel DBS leads (NuMed) implanted in STN and GP, respectively and a Utah 96-channel microelectrode array (1.5mm depth, Blackrock) implanted in the arm area of M1. Recordings were performed once or twice after each MPTP injection with the animal in a resting, awake state, determined by eye and contralateral arm motion captures.

Data processing: All analysis was performed using MATLAB scripts. Each session of LFP data was filtered to 3kHz and segmented into 12s duration segments. Only resting-awake data was kept, differentiated from sleeping states through eye monitoring. The power spectral density (PSD) was used to identify changes in power, both in low-beta (8-20 Hz) and high-beta (21-35 Hz), and in different brain structures across states, as calculated for each segment in MATLAB. In order to compare beta oscillations, I normalized each segment using z-scores and utilized these scores for analysis.

Results

Changes in low beta-band oscillations throughout the network. There is a progressive increase in low beta-band power in the STN and GP while there was overall decrease in M1 (Fig 1).

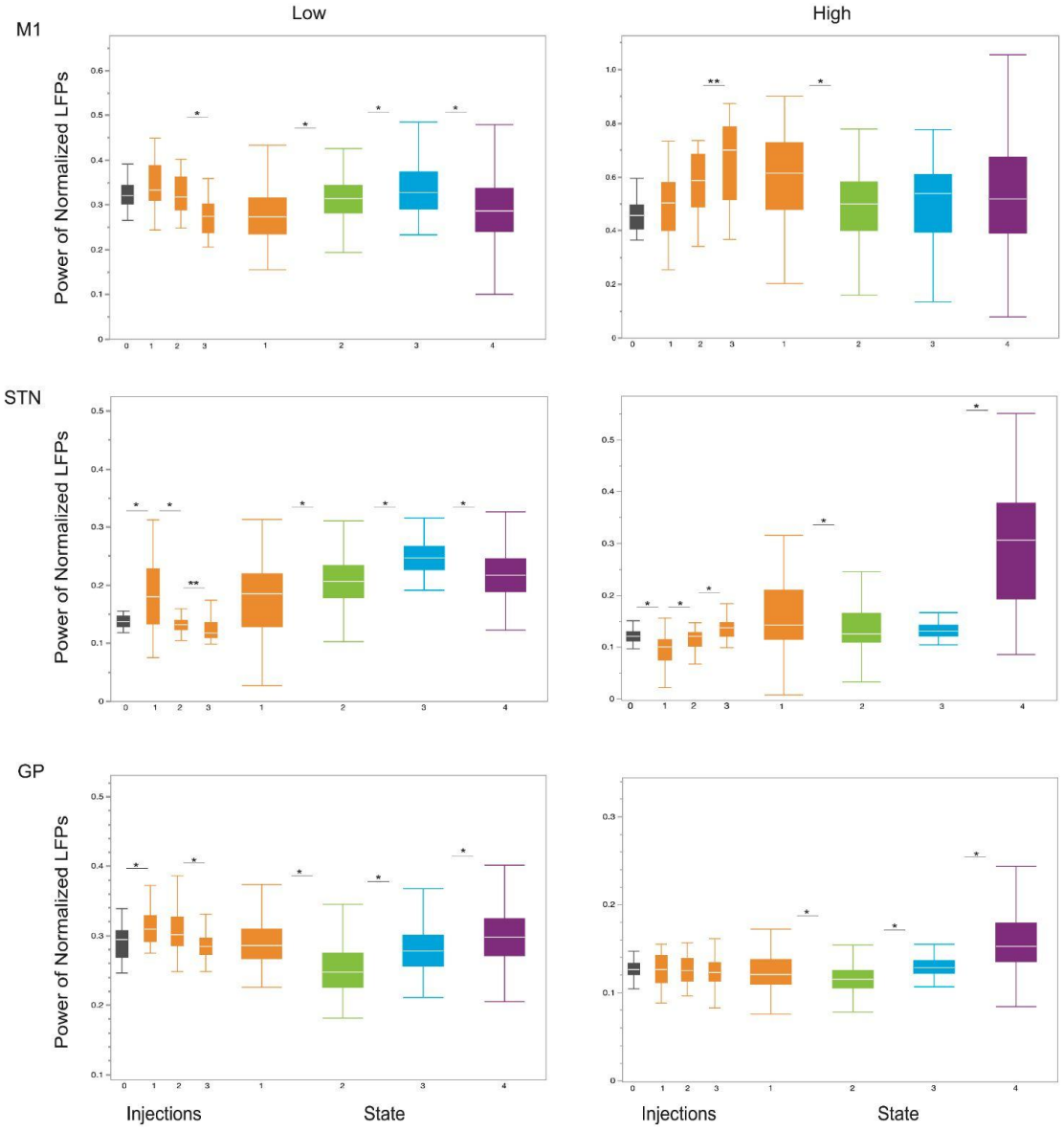

Figure 1: Changes in power with increasing parkinsonism severity. Low (8-20 Hz) and high (21-35 Hz) for each site by first three injections then by state. Wilcoxon one-way tests; *p<0.01, **p<0.05.

Distinct changes in low and high beta-band oscillations. There is a progressive increase in STN and GP high beta activity and no change in M1 (Fig 1). This difference suggests the possibility of distinct roles of both low and high beta power changes in the development of parkinson's disease.

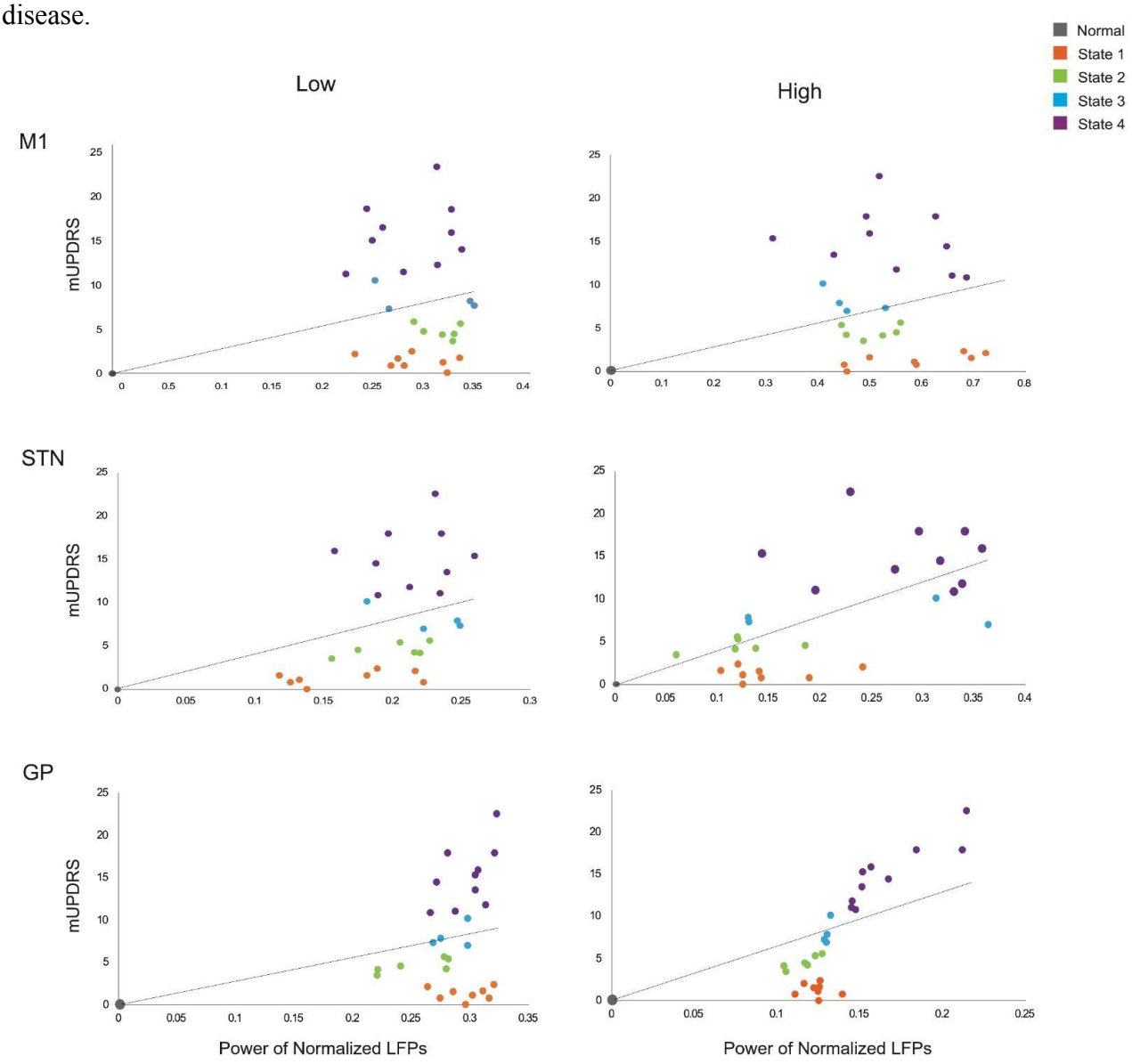

Figure 2: Changes in parkinsonian severity determined by mUPDRS with scores.

Changes in beta-band oscillatory activity precede the onset of parkinsonism motor symptoms. Significant changes across in low-beta band activity the network occurred as motor symptoms

progressed. There is an increase in STN and GP power with mUPDRS and there are significant changes early in parkinsonism (Fig 1,2). These changes are important in identifying beta-band oscillations as a biomarker for PD.

Conclusion

These findings support a link between changes in beta-band oscillations in the BGTC network and motor symptoms of PD, with the independent changes in low and high beta bands. These results also imply an impact of beta-band oscillation disruption on the ability of the BGTC network to encode sensory-motor information, thus inducing PD symptoms. Finally, these results emphasize the importance of utilizing a holistic approach in analyzing temporal changes of beta oscillations to better identify biomarkers for potential symptom characterization.

Future analysis of these results in another animal is important to understanding if these changes are consistent in all patients. Further future research in oscillatory changes with specific behavioral/movement epochs and coherence between the subcortical and cortical regions are also important steps in understanding changes in beta band oscillations as a biomarker for PD.

Resources

1. Xia, R., & Mao, Z.-H. (2012). Progression of motor symptoms in Parkinson's disease. Neuroscience Bulletin, 28(1), 39–48. https://doi.org/10.1007/s12264-012-1050-z
2. Utter, A. A., & Basso, M. A. (2008). The basal ganglia: An overview of circuits and function. *Neuroscience & Biobehavioral Reviews*, *32*(3), 333–342. https://doi.org/10.1016/j.neubiorev.2006.11.003
3. Leblois, A., Meissner, W., Bioulac, B., Gross, C. E., Hansel, D., & Boraud, T. (2007). Late emergence of synchronized oscillatory activity in the pallidum during progressive parkinsonism. *European Journal of Neuroscience*, *26*(6), 1701–1713. https://doi.org/10.1111/j.1460-9568.2007.05777.x
4. Khanna, P., & Carmena, J. M. (2017). Beta band oscillations in motor cortex reflect neural population signals that delay movement onset. *ELife*, *6*. https://doi.org/10.7554/elife.24573
5. Engel, A. K., & Fries, P. (2010). Beta-band oscillations—signalling the status quo? *Current Opinion in Neurobiology*, *20*(2), 156–165. https://doi.org/10.1016/j.conb.2010.02.015
6. Ray, N. J., Jenkinson, N., Wang, S., Holland, P., Brittain, J. S., Joint, C., Stein, J. F., & Aziz, T. (2008). Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. *Experimental Neurology*, *213*(1), 108–113. https://doi.org/10.1016/j.expneurol.2008.05.008
7. Kuhn, A. A., Kempf, F., Brucke, C., Gaynor Doyle, L., Martinez-Torres, I., Pogosyan, A., Trottenberg, T., Kupsch, A., Schneider, G.-H., Hariz, M. I., Vandenberghe, W., Nuttin, B., & Brown, P. (2008). High-Frequency Stimulation of the Subthalamic Nucleus Suppresses Oscillatory Activity in Patients with Parkinson's Disease in Parallel with Improvement in Motor Performance. *Journal of Neuroscience*, *28*(24), 6165–6173. https://doi.org/10.1523/jneurosci.0282-08.2008